Computerized Systems

The AGIT Paper "Change Management and Risk Assessment of validated computerized systems in a GLP environment, v1.0" describes the responsibility of QA during the change management process (page 10). Would you consider a scaled approach to QA involvement (risk based), with justification, based on whether the system changes are of low (validation status remains unchanged), medium or high impact?

The degree of QA involvement should be described in an SOP. A scaled approach is possible. All actions and documentation of the change management process should be covered by QA, since even changes with a low impact have an execution step, function tests and documentation. System changes with high impact will require more involvement of QA.

Original text from AGIT guideline "Change Management and Risk Assessment of validated computerized systems in a GLP environment, v1.0", p.10:

The **Quality Assurance (QA)** should be integrated in the change management process. The QA involvement should be described in an SOP. The following topics should be addressed:
· Information process on planned activities
· Review of documents (e.g. test plan, test report)
· Inspection of activities.

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Is validation expected for the application of standard software used for data evaluation (for example XLFit; Parallel Line Assay)?

The concern is that the validation team may not have access to a detailed test data set to thoroughly test the system.

Yes; all computerized systems should be validated at least to the extent that they are used in the GLP environment, i.e. for the user requirements for this application. If no test data set is available from the vendor, a validation can be made based on a set of existing data that are once evaluated by the software to be validated and once by other means. In this case, the data used for the validation should cover the foreseen range of application.

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Study Plan

When commercial software is used that has different options for data evaluation, how detailed should the description be in the Study Plan (is software name and version sufficient or must the evaluation parameters to prevent bias be stated)? Is the advice different for software such as Excel than for scientific software (e.g. Parallel Line Analysis (PLA))?

The study plan should - in addition to software name and version – include the parameters for data evaluation or instructions how the evaluation should be done and documented. It can also refer to an SOP on data evaluation or give a set of criteria that have to be considered for chosing appropriate parameters.

Amendment to Study Plan

If the experimental completion date changes due to delay of the experimental phase of the study, is it necessary that this is amended? Is it possible to address the change only as a deviation (since the event already happened and an amendment cannot actually be used as a planning tool)?

A study plan amendment is needed for planned changes, i.e. when the study director knows that the schedule will be delayed. It will also be used to inform others about the new schedule.

If a delay is only recognized afterwards, it is possible to handle it as a deviation. This deviation should be mentioned in the final report.

Test Item:

If the Test Item is returned to Sponsor at the end of the study, must the Test Facility retain a sample? (This can increase potential for contamination or cause safety issues for hazardous test items in terms of handling and storage.)

According to OGLP 6.2.6 and 10 a sample for analytical purposes from each batch of test item should be retained for all studies except short-term studies in the archives for at least ten years after study completion.

In case the sponsor has a GLP archive, this should be stated in the study report. If the sponsor's archive is not under the supervision of a GLP monitoring program (as part of a test facility or only as an archive), the archiving period in this archive should be excluded in the GLP statement of the study director. (Interpretation 10.11)

Reference Item

For a biological assay, the reference item is often a "known" concentration of the same compound as the test item which will be used to determine the relative concentration of the test item. As a CRO, we receive the reference with a just a supplier code (often an internal Sponsor number) and no COA or other documentation.

- Is some form of characterisation check required to be performed by the CRO (if so is there any guidance)?
- What information should QA expect to find in the data to confirm the identity of the reference item?

The OGLP outlines the information required for a reference item, which should also be available for the QA to be able to confirm the identity of the reference item:

- *Characterisation each test and reference item should be appropriately identified (e.g. code, Chemical Abstracts Service Registry Number [CAS number], name, biological parameters). For each study, the identity, including batch number, purity, composition, concentrations, or other characteristics to appropriately define each batch of the test or reference items should be known. The stability of test and reference items under storage and test conditions should be known for all studies (OGLP).*
- *In the case that no expiry date is available this must be stated, justified in the final report and excluded from the GLP Compliance Statement (Interpretation 6.4).*

According to Advisory Document No. 11 (*The Role and Responsibilities of the Sponsor in the Application of the Principles of GLP): In cases where the test item is supplied by the sponsor, there should be a mechanism, developed in co-operation between the sponsor and the test facility, to verify the identity of the test item subject to the study.*

This applies also for reference items.

Quality Assurance

Is it appropriate for QA to be the author of or be responsible for general SOPs such as QC, SOP production/distribution, method validations, and equipment qualification procedures? These are general procedures that QA personnel do not themselves perform (or only part of the procedure) but QA may have a greater understanding of the regulatory expectations than scientific staff or management.

There are no restrictions regarding who writes or contributes to SOPs.

Standard Operating Procedures are documented procedures which describe how to perform tests or activities normally not specified in detail in study plans or test guidelines, therefore they should be written and/or reviewed by personnel who has very good knowledge of the activities described. QA personnel are not normally involved in drafting SOPs; however it is desirable that they review SOPs before use in order to assess their clarity and compliance with GLP Principles. (OECD No. 4)

Peer Review Correspondence

In OECD Advisory Document no. 16 (pathology peer review), it is stated that all correspondence regarding the histopathological evaluation of the slides used for peer review between the sponsor and representatives of the test facility and the peer review pathologist should be retained in the study file, including minutes of teleconferences between the sponsor and the test facility.

From the Advisory Document it can be interpreted that the test facility is finally responsible for the retention of respective correspondence.

Would it be appropriate that if the Peer Reviewer is not located at the test facility to define in the Peer Reviewer's SOPs that all correspondence will be archived by the test facility and not at test site of the peer review pathologist?

Is it sufficient to only define this in the Study Plan?

Since this correspondence is considered to be part of the study file, the same requirements regarding archiving as for the study documentation apply. It has to be clear in the associated documents (study plan, SOPs etc.) where this information can be retrieved and it should be available in due time in case of a study audit request.

Final Report

As per GLP principles, "the storage location of the study plan, samples of test and reference items, specimens, raw data and the final report are to be specified in the final report". Historically, the "location" was interpreted to be a physical location.

- To what level of detail must this location be referenced (Company name/city/Country) or more detailed?
- For electronic final reports and/or electronic raw data stored in a cloud or via an external storage providor, what physical location should be provided? (In a cloud environment, this could easily change and would not be transparent to the SD).
- Do amendments to the report have to be written each time a location changes?
- Could one state under who's responsibility the materials are stored rather than a physical location?

The description of the location should be sufficient to permit access to the study specific documents or samples and depends on the test facility situation. It is e.g. acceptable to indicate "stored in the GLP archive of (or at) the test facility", since the name and address of the test facility are indicated in the final report. In the case of storage at a contracted archive, the name, city and country of the place or of the archive owner is expected.

In the case of e-archiving, the name and address of the test facility should be mentioned. In case of external storage of electronic documents, also the name and address of the e-archive service provider should be available.

When a storage location changes there should be a documentation allowing to identify the new location. This can be an amendment to final report. In case of a huge amount of final reports, for justified reasons and in agreement with the notification authority, a document can be established which is signed by the test facility management, instead of an individual amendment per report. The document has to describe the transfer as well as the location of the new archive including the date of transfer. The document has to be kept by the undersigned person and in the new archive (Original). Furthermore a copy of the document needs to be sent to the competent authority. (Interpretation 10.9)

Study Conduct (Handling of electronic data)

Re-calculation of Bioanalytical Data : Re-calculation of bioanalytical data is sometimes required by registration authorities. If the bioanalytical raw data has been defined to be paper instead of the original electronically acquired data, how are these re-analyses to be performed (Manual entry to analysis software? Reversion to original e-data?)

It is possible to use original e-data, but it should be verified that these data are identical with the original raw data on paper. This check should be documented and eventually justified.

Currently it is accepted that for electronic data the paper printouts are defined as GLP raw data. Often companies still retain additionally the electronic data in the system or on a separate server. What are the expectations concerning the retention of electronic data in bioanalytical labs especially data derived from e.g. acquisition software like Analyst?

These additional electronic data are not considered GLP raw data according definition. Obviously, the printed data have to contain all information, not only the measured raw data, but also methods, acquisition parameters, measuring sequences and so on. Therefore, there are no requirements regarding storage of the same data in electronic form.

Amendment to Final Report:

When issuing an Amendment to Final Report (only formal changes): Must a “GLP Statement of Compliance” signed by the Study Director be included in addition to the “GLP Quality Assurance Statement” signed by the QA?

Amendment to final report should state the reason for the correction and be dated and signed by the study director. In case of formal change no GLP statement of compliance is expected.

Amendment to Final Report:

A Sponsor requested to amend a report due to addition of results from calculations which were based on existing raw data (only additional derived data is added, no additional raw data has been created).

How many amendments to Final Report are needed in this case? Is it enough to release only one Amendment with the added results from calculations or is it expected to have 2 Amendments: First Amendment (as a planning tool), introducing the need for the new calculations and Second Amendment – with the additional results from the calculations?

If only one report amendment is required, how do we justify that additional calculations were made prior to report amendment signature? How would QA be informed?

Additional results based on calculation, without experimental activity, can be documented with only one amendment. QA should review the data and issue an QA statement that is part of the amendment.

Archival

In what time frame after finalization of the final report do all of the study related materials/documents need to be physically or in the case of e-data electronically in their respective archives?

Is there an expectation from Swiss GLP Monitoring Authorities or may this simply be defined in the facility's SOP?

Consensus document No 8 indicates "in a timely manner". This time depends on the complexity of the study and it is not reasonable to establish a global time frame. According to Advisory Document No. 15 the Study Director is responsible for ensuring that during or immediately after completion (including termination) of a study, all study related records and materials are transferred to the archive(s).

The expectation from the Swiss GLP Monitoring would be two to four weeks. It is important that the study director plans sufficient time at the end of the study to organise all raw data and materials. Once all study specific data are assembled, the study director should transfer them to the archivist.

It is recommended to define a (study specific) time frame in the facility's SOP.

General Questions

Is there any initiative to "modernize" the OECD Principles of GLP (OECD1) (e.g. the Master schedule sheet is not an effective planning tool)
Currently, there are no initiatives to update the OECD Principles of GLP. However, the Principles are further developed in OECD documents 2-n as well as supporting documents such as FAQ (see: http://www.oecd.org/env/ehs/testing/glp-frequently-asked-questions.htm)

Is more information available on the SEND format required by the US registration authorities?
No further information regarding SEND format is currently available.
BUT: http://www.cdisc.org/send
"The CDISC SEND Team is always interested in your comments or questions. Any feedback regarding SEND can be submitted through the CDISC Discussion forum."